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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Ester FRIDE *et al.*	Confirmation No.:	6091
Application No:	09/698,071	Group Art Unit:	1621
Filing Date:	October 30, 2000	Examiner:	Samuel A. Barts
For:	AGONISTS SPECIFIC FOR THE PERIPHERAL CANNABINOID RECEPTOR	Attorney Docket No.:	87754-7100

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

As noted in the Amendment filed April 13, 2004, enclosed for further examination in the above-identified application is a Declaration of Raphael Mechoulam Under 37 C.F.R. § 1.132 in support of the patentability of the claims.

No fee is believed to be due in connection with this filing. Should any fees be required, please charge such fees to Winston & Strawn LLP Deposit Account No. 50-1814.

Respectfully submitted,

5/13/04
Date

Jeffrey A. Wolfson (Reg. No. 42,234)

WINSTON & STRAWN LLP
Customer No. 28765

202-371-5904

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Ester FRIDE et al.	Confirmation No.:	6091
Application No.:	09/698,071	Group Art Unit:	1621
Filed:	October 30, 2000	Examiner:	S. Barts
For:	AGONISTS SPECIFIC FOR THE PERIPHERAL CANNABINOID RECEPTOR	Attorney Docket No.:	87754-7100

DECLARATION OF RAPHAEL MECHOULAM UNDER 37 C.F.R. § 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I am a co□inventor, together with Ester Fride, Aviva Breuer, Lumir Hanuš, Susanna Tchilibon, Michal Horowitz and Aaron Garzon, of the subject matter claimed in the above□referenced U.S. patent application. I am a citizen of Israel and currently reside at 12 Tchernihovsky Street , Jerusalem 92581, Israel.

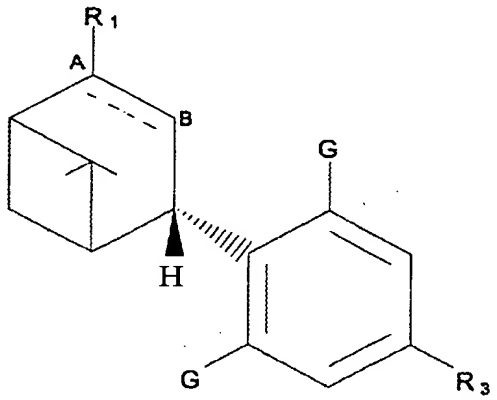
2. I received my Ph.D. degree from the Weizmann Institute of Science, Rehovot, Israel, in 1958, and am currently an employee of the Hebrew University of Jerusalem, Israel, where I am a full professor in the School of Pharmacy.

3. Yissum Research Development Company ("Yissum"), an Israeli company having a place of business at Hi-Tech Park, Edmond J. Safra Campus, Givat-Ram, P. O. Box 39135, Jerusalem 91390, Israel, is a wholly-owned subsidiary of the Hebrew University of Jerusalem and is the exclusive assignee of the University's know-how and intellectual property. I have worked in research in the Hebrew University of Jerusalem since 1966.

4. My present title is Lionel Jacobson Professor of Medicinal Chemistry at the Hebrew University of Jerusalem, and I have held this position for almost thirty years, since 1975. I have over forty years of experience in the research, synthesis, testing, and development of new compounds, compositions, and methods of making and using the same. Since the beginning of my career, I have published almost 300 scientific articles in highly regarded journals and books, and have presented my achievements at many international scientific conferences. Most of these publications deal with chemistry, pharmacology and clinical effects of plant, synthetic and mammalian cannabinoids. I was the first to identify the psychotropically active constituent in marijuana (delta-9-tetrahydrocannabinol) as well as the first active endocannabinoid in brain (anandamide). I am a member of several scientific societies and was elected a member of the Israel Academy of Sciences in 1994. Attached are my curriculum vitae and list of publications.

5. I have reviewed and understand the above-identified patent application, the pending claims, the Office Action, and the reference cited therein. In particular, I am a co-inventor on the reference cited, namely U.S. Patent No. 5,434,295 to Mechoulam et al. ("Mechoulam-'295"). I have been asked to give my opinion regarding the testing and superior activity of one of the claimed compounds and the claimed methods.

6. The above-identified application is directed to compounds, compositions, and CB2 agonists having the structure:



having the (3S,4S) configuration, each of which is essentially free of the (3R,4R) enantiomer, wherein:

A---B designates an optional double bond,

R_1 is -R'OR"' wherein R' is C_1-C_5 straight or branched chain alkyl and R"' is hydrogen or C_1-C_5 alkyl;

G is $-OR_2$ wherein R_2 is C_1-C_5 straight or branched chain alkyl; and

R_3 is a straight chain or branched -C_5-C_{12} alkyl.

The above-identified application provides an *in vitro* example of the preferential binding to the CB2 receptor using the disclosed compounds, particularly for the compound HU-308 where R_1 is $-CH_2OH$, G is $-OCH_3$, and R_3 is 1,1-dimethyl heptyl.

7. Mechoulam-'295 does not teach the specific compounds, compositions, and CB2 agonists that are presently claimed. Rather, Mechoulam-'295 discloses a genus of compounds but fails to teach about the abilities of any of these compounds to bind to CB1 or CB2 receptors.

8. Receptor Binding Assays: As noted in the present application on page 21, the CB1 binding assays were performed with synaptosomal membranes prepared from rat brains (Devane, W.A., Hanus, L., et al., *Science* 258, 1946-1949 (1992)). The CB2 assays were performed with transfected cells (Mechoulam, R., Ben-Shabat, S., et al., *Biochem. Pharmacol.* 50, 83-90 (1995)). HU-308, however, did not bind to CB1 under the conditions tested. The probe [^{3}H]HU-243 was employed in a centrifugation based ligand binding assay (Devane, W.A., Hanus, L., et al., and Devane, W.A., Breuer, A., et al., *J. Med. Chem.* 35, 2065-2069 (1992)).

9. HU-308 was demonstrated to preferentially bind to the CB2 cannabinoid receptor. HU-308 binds to the CB2 cannabinoid receptor with a Ki = 22.7 ± 3.9 nM, as measured by competitive inhibition of [^{3}H]HU-243 in COS-7 cells transfected with plasmids expressing the CB2 receptor gene (Mechoulam, R., Ben-Shabat, S., et al., *Biochem. Pharmacol.* 50, 83-90 (1995)). HU-308, however, did not bind to CB1, under the conditions tested. This 400-fold difference in binding was reflected in the results of the pharmacological assays, as shown in FIG. 3 of the above-identified application. A copy of FIG. 2 is attached hereto. By comparison, the CB2/CB1 affinity ratio of HU-259 was only 10 and the ratio of HU-255 was only 6.

10. HU-308 was also shown as acting to reduce blood pressure, block defecation, and elicit anti-inflammatory and peripheral analgesic activity. The hypotensive, anti-inflammatory, peripheral analgetic activity and gastrointestinal effects produced by HU-308 are blocked by the CB2 antagonist SR 144528, but not by the CB1 antagonist SR 141716A.

11. The superior preferential CB2 binding of HU-308 was also confirmed in International PCT Publication WO 03/063758 (PCT/IL03/00077), which was filed after the above-captioned application. The data from Table 1 shows that the IC_{50} of HU-308 for CB2 was 13.3 nM and for CB1 receptors was 3600 nM, thus providing a CB2/CB1 IC_{50} ratio of more than 270. A copy of this Table 1 and accompanying text on pages 46-49 from the PCT publication is attached hereto.

12. As one of ordinary skill in the art, based on my review of the claimed invention and superior properties of HU-308 compared to the closest prior art, it is my opinion and judgment that the invention as currently claimed provides a surprising and unexpected result. In particular, the surprising and unexpected result obtained was the superior preferential binding of HU-308 to the CB2 receptor, *e.g.*, HU-308 does not bind to CB1, but efficiently binds to CB2 (Ki = 22.7 ± 3.9 nM).

13. I further declare that all statements made herein of my knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: 5 May, 2004 R. Mechoulam

Printed Name: Raphael Mechoulam
Title: Professor of Medicinal Chemistry
at The Hebrew University of Jerusalem

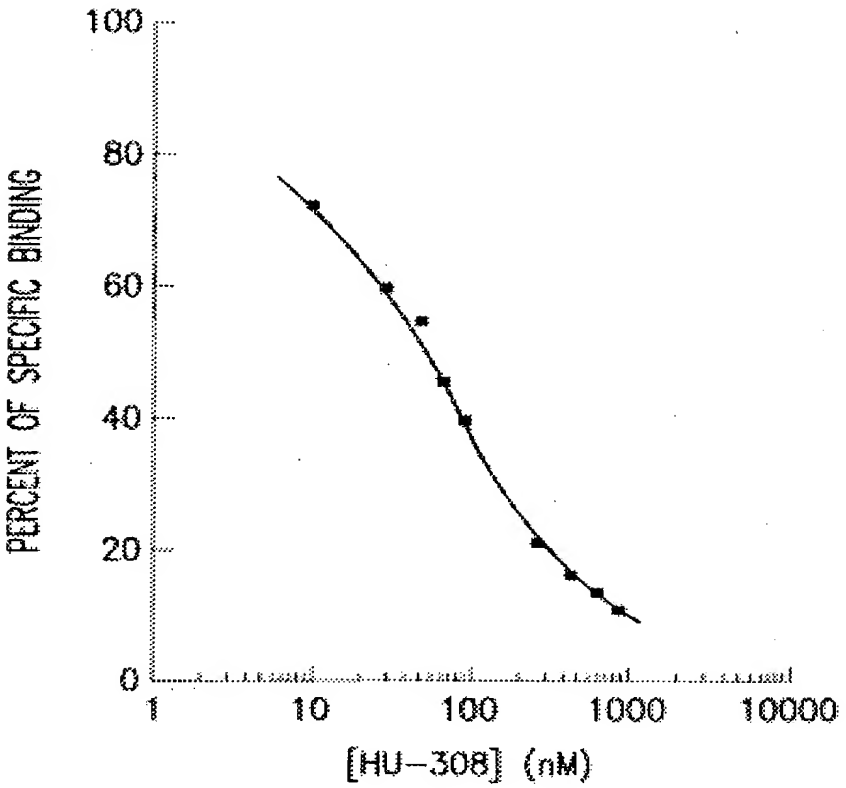


FIG.2

Professor Raphael Mechoulam

1930	Born Sofia, Bulgaria
1952	M.Sc. in Biochemistry, Hebrew University, Jerusalem
1953-56	Army Service
1956-58	Ph.D. studies with Professor F. Sondheimer, Weizmann Institute, Rehovot. Research on steroid synthesis.
1959-60	Postdoctoral research at Rockefeller Institute, New York. Research on the structure of triterpenes.
1960-65	Junior and later Senior Scientist, Weizmann Institute. Resesearch on chemistry of natural products, including cannabinoids, terpenes, alkaloids.
1966-	Hebrew University, Jerusalem; 1968 – Associate Professor; 1972 – Professor.
1975-	Endowed chair: Lionel Jacobson Professor of Medicinal Chemistry.
1979-82	Rector (Academic Head) of Hebrew University.
1983-85	Pro-Rector, Hebrew University.
1993-94	Visiting Professor, Department of Pharmacology, Medical College of Richmond.
1999-2000	President of the International Cannabinoid Research Society.

Research interests: chemistry and biological activity of natural products and synthetic drugs.

Honors

Somach Sachs Prize for "best research by a scientist below 35 at the Weizmann Institute". 1964.

Distinguished Visiting Professorship, Ohio State University, Columbus, Ohio, 1982-1983.

International Biannual Cannabis meeting (held in Colymbari, Crete), 1990, dedicated to R.M.

"Pharmacology, Biochemistry and Behavior" Nov. 1991 issue dedicated to R.M. for achievements in the cannabinoid field.

Kolthof Prize in Chemistry, 1994, The Technion, Haifa.

Elected, Member Israel Academy of Sciences, 1994.

Hanf prize, Germany, 1997, for "the discovery of THC and lasting research on Cannabis – anandamides".

Hanus Medal, 1998, by Czech Chemical Society in recognition of contribution to cannabinoid chemistry.

David R. Bloom Prize, 1998, for "excellence in pharmaceutical research", Hebrew University.

The International Cannabinoid Research Society (ICRS) establishes an annual award to be named The R. Mechoulam Annual Award in Cannabinoid Research, 1999.

Israel Prize in Exact Sciences – chemistry, 2000.

Ariens Award and Lecture. 2000. Dutch Pharmacological Society sponsored by Solvay Pharmaceuticals. Amsterdam.

Honorary Degree Doctor of Science. 2001. Ohio State University, Columbus, Ohio.

Elected, Honorary Member of the Israel Society of Physiology and Pharmacology. 2002.

Name lectures:

Copenhagen, Denmark. 1977. Ferosan Lecture. School of Pharmacy.

Tuscon, Arizona, 1983, Golden Headed Cane Memorial Lecture. Faculty of Medicine.

Stockholm, Sweden, 1994, Ulf von Euler Lecture in Physiology, Karolinska Institute.

Maale Hamisha, 2000, Magnes Memorial Lecture, Israel Society for Physiology and Pharmacology.

Raphael Mechoulam

List of publications

Summaries of lectures at scientific meetings are not included.

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9. F. Sondheimer and R. Mechoulam. The Diels-Alder reaction of steroidal 20-methylene-Δ^{16}-pregnene derivatives with maleic anydride. J. Org. Chem., 24, 106-107, (1959).

10. F. Sondheimer, S. Burstein and R. Mechoulam. Synthesis in the cardiac aglycone field. The conversion of 14α to a 14β hydroxy

group in the androstane series. The ultraviolet spectra of Δ^{15}-androstene-17-ones. J. Amer. Chem. Soc., 82, 3209-3214 (1961).

11. F. Sondheimer, R. Mechoulam and M. Shprecher. 19-Hydroxy-10-isotestosterone. Tetrahedron Letters, 38-44 (1960).

12. R. Mechoulam, F. Sondheimer, A. Melera and F.A. Kincl. The structure of zapotidine. J. Amer. Chem. Soc. 83, 2022 (1961).

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b) Structure-Activity Relationships in the Cannabinoid Series – R. Mechoulam and H. Edery, pp. 101-136.

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